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☐	L1	liu-c$.in. or mazumder-A$.in. or Brush-C$.in. or johnson-T$.in.	7041
☐	L2	hydrogel same probe	308
☐	L3	L2 and (hybridiz$ near target)	74
☐	L4	L2 and (hybridiz$ near (target or nucleic acid or protein or DNA or RNA))	97
☐	L5	L4 and (photocycloaddition)	3
☐	L6	L2 and photocycloaddition	10
☐	L7	L6 and (nucleic acid or protein or DNA or RNA)	10
☐	L8	l1 and l2	13
☐	L9	photocycloaddition	190
☐	L10	L9 and (hydrogel or polyacrylamide or polyurethane)	60
☐	L11	L10 and probe	36

END OF SEARCH HISTORY

L11: Entry 21 of 36 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329139 B1
TITLE: Automated sorting system for matrices with memory

Detailed Description Text (8):
As used herein, a matrix refers to any solid or semisolid or insoluble support on which a code is to which the memory device and/or the molecule of interest, typically a biological molecule, organic molecule or biospecific ligand is linked or contacted. Typically a matrix is a substrate material having a rigid or semi-rigid surface. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different polymers with, for example, wells, raised regions, etched trenches, or other such topology. Matrix materials include any materials that are used as affinity matrices or supports for chemical and biological molecule syntheses and analyses, such as, but are not limited to: polystyrene, polycarbonate, polypropylene, nylon, glass, dextran, chitin, sand, pumice, polytetrafluoroethylene, agarose, polysaccharides, dendrimers, buckyballs, polyacrylamide, Kieselguhr-polyacrylamide non-covalent composite, polystyrene-polyacrylamide covalent composite, polystyrene-PEG [polyethyleneglycol] composite, silicon, rubber, and other materials used as supports for solid phase syntheses, affinity separations and purifications, hybridization reactions, immunoassays and other such applications. The matrix herein may be particulate or may be in the form of a continuous surface, such as a microtiter dish or well, a glass slide, a silicon chip with a surface adapted for linking of biological particles or molecules, a nitrocellulose sheet, nylon mesh, or other such materials. When particulate, typically the particles have at least one dimension in the 5-10 mm range or smaller. Such particles, referred collectively herein as "beads", are often, but not necessarily, spherical. Such reference, however, does not constrain the geometry of the matrix, which may be any shape, including random shapes, needles, fibers, elongated, etc. The "beads" may include additional components, such as magnetic or paramagnetic particles [see, e.g., Dyna beads (Dynal, Oslo, Norway)] for separation using magnets, fluophores and other scintillants, as long as the additional components do not` interfere with chemical reactions, data entry or retrieval from the memory.

Detailed Description Text (9):
Also contemplated herein, are the combination of "chips" or arrays that contain hundreds of thousands of probes [see, e.g., U.S. Pat. No. 5,525,531] linked to a matrix with a surface suitable for linking probes or other selected molecules or biological particles.

Detailed Description Text (50):
As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography [TLC], mass spectrometry [MS], size exclusion chromatography, gel electrophoresis, particularly agarose and polyacrylamide gel electrophoresis [PAGE] and high performance liquid chromatography [HPLC], used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure

compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

Detailed Description Text (56):
As used herein, Southern, Northern, Western and dot blot procedures refer to those in which DNA, RNA and protein patterns, respectively, are transferred for example, from agarose gels, polyacrylamide gels or other suitable medium that constricts convective motion of molecules, to nitrocellulose membranes or other suitable medium for hybridization or antibody or antigen binding are well known to those of skill in this art [see, e.g., Southern (1975) J. Mol. Biol. 98:503-517; Ketner et al. (1976) Proc. Natl. Acad. Sci. U.S.A. 73:1102-1106; Towbin et al. (1979) Proc. Natl. Acad. Sci. U.S.A. 76:4350.

Detailed Description Text (79):
Matrices include any material that can act as a support matrix for attachment of the molecules or biological particles of interest and can be in contact with or proximity to or associated with, preferably encasing or coating, the data storage device with programmable memory. Any matrix composed of material that is compatible with and upon or in which chemical syntheses are performed, including biocompatible polymers, is suitable for use herein. The matrix material should be selected so that it does not interfere with the chemistry or biological reaction of interest during the time which the molecule or particle is linked to, or in proximity therewith [see, e.g., U.S. Pat. No. 4,006,403]. These matrices, thus include any material to which the data storage device with memory can be attached, placed in proximity thereof, impregnated, encased or otherwise connected, linked or physically contacted. Such materials are known to those of skill in this art, and include those that are used as a support matrix. These materials include, but are not limited to, inorganics, natural polymers, and synthetic polymers, including, but are not limited to: cellulose, cellulose derivatives, acrylic resins, glass that is derivatized to render it suitable for use a support, silica gels, polystyrene, gelatin, polyvinyl pyrrolidone, co-polymers of vinyl and acrylamide, polystyrene cross-linked with divinylbenzene or the like [see, Merrifield (1964) Biochemistry 3:1385-1390], polyacrylamides, latex gels, polystyrene, dextran, polyacrylamides, rubber, silicon, plastics, nitrocellulose, celluloses, natural sponges, and many others. It is understood that the matrix materials contemplated are those that are suitable for use a s support matrix for retaining molecules or biological particles during syntheses or reactions.

Detailed Description Text (122):
Synthetic matrices include, but are not limited to: acrylamides, dextran-derivatives and dextran co-polymers, agarose-polyacrylamide blends, other polymers and co-polymers with various functional groups, methacrylate derivatives and co-polymers, polystyrene and polystyrene copolymers [see, e.g., Merrifield (1964) Biochemistry 3:1385-1390; Berg et al. (1990) in Innovation Perspect. Solid Phase Synth. Collect. Pap., Int. Symp., 1st, Epton, Roger (Ed), pp. 453-459; Berg et al. (1989) in Pept. Proc. Eur. Pept. Symp., 20th, Jung, G. et a. (Eds), pp. 196-198; Berg et al. (1989) J. Am. Chem. Soc. 111 :8024-8026; Kent et al. (1979) Isr. J. Chem. 17:243-247; Kent et al. (1978) J. Org. Chem. 43:2845-2852; Mitchell et al. (1976) Tetrahedron Lett. 42:3795-3798; U.S. Pat. No. 4,507,230; U.S. Pat. No. 4,006,117; and U.S. Pat. No. 5,389,449]. Methods for preparation of such matrices are well-known to those of skill in this art.

Detailed Description Text (124):
For example, U.S. Pat. No. 5,403,750, describes the preparation of polyurethane-based polymers. U.S. Pat. No. 4,241,537 describes a plant growth medium containing a hydrophilic polyurethane gel composition prepared from chain-extended polyols; random copolymerization is preferred with up to 50% propylene oxide units so that the prepolymer will be a liquid at room temperature. U.S. Pat. No. 3,939,123 describes lightly crosslinked polyurethane polymers of isocyanate terminated

prepolymers containing poly(ethyleneoxy) glycols with up to 35% of a poly (propyleneoxy) glycol or a poly(butyleneoxy) glycol. In producing these polymers, an organic polyamine is used as a crosslinking agent. Other matrices and preparation thereof are described in U.S. Pat. Nos. 4,177,038, 4,175,183, 4,439,585, 4,485,227, 4,569,981, 5,092,992, 5,334,640, 5,328,603

Detailed Description Text (133):
A large variety of methods are known for attaching biological molecules, including proteins and nucleic acids, molecules to solid supports [see. e.g., U.S. Pat. No. 5,451,683]. For example, U.S. Pat. No. 4,681,870 describes a method for introducing free amino or carboxyl groups onto a silica matrix. These groups may subsequently be covalently linked to other groups, such as a protein or other anti-ligand, in the presence of a carbodiimide. Alternatively, a silica matrix may be activated by treatment with a cyanogen halide under alkaline conditions. The anti-ligand is covalently attached to the surface upon addition to the activated surface. Another method involves modification of a polymer surface through the successive application of multiple layers of biotin, avidin and extenders [see, e.g., U.S. Pat. No. 4,282,287]; other methods involve photoactivation in which a polypeptide chain is attached to a solid substrate by incorporating a light-sensitive unnatural amino acid group into the polypeptide chain and exposing the product to low-energy ultraviolet light [see, e.g., U.S. Pat. No. 4,762,881]. Oligonucleotides have also been attached using a photochemically active reagents, such as a psoralen compound, and a coupling agent, which attaches the photoreagent to the substrate [see, e.g., U.S. Pat. No. 4,542,102 and U.S. Pat. No. 4,562,157]. Photoactivation of the photoreagent binds a nucleic acid molecule to the substrate to give a surface-bound probe.

Detailed Description Text (159):
If needed, segregation of the binding and information surfaces can be achieved by coating portions of the OMD with films formed from a dielectric material such as polyethylene, MYLAR, TEFLON.RTM., KAPTON, polycarbonate, or, preferably, the para-xylylene polymers sold under the trade name Parylene [see, e.g., U.S. Pat. Nos. 3,288,728, 3,342,754 and 3,429,739], or any other such materials that are commonly used in the electronics industry to passivate electronic components and circuit boards, and as a coating for medical devices, especially implants, catheters, probes and needles. [Parylene is the trade name for members of a series of polymers which are commercially available from Specialty Coating Systems, Inc., of Indianapolis, Ind. and originally from Union Carbide Corporation, Greenville, S.C., see, U.S. Pat. Nos. 3,288,728, 3,342,754 and Gorham 3,429,739; see, also brochures distributed by the manufacturer, entitled "Parylene Conformal Coatings Specifications and Properties" (.COPYRGT. 1984, Specialty Coating Systems, Inc.), and "Parylene, A Biostable Coating for Medical Applications" (.COPYRGT. 1984, Specialty Coating Systems, Inc.]. These polymers provide a conformal biostable coating which electrically and chemically isolates the protected surface from its environment.

Detailed Description Text (428):
Typically, SPA uses fluomicrospheres, such as diphenyloxazole-latex, polyacrylamide-containing a fluophore, and polyvinyltoluene [PVT] plastic scintillator beads, and they are prepared for use by adsorbing compounds into the matrix. Also fluomicrospheres based on organic phosphors have been developed. Microplates made from scintillation plastic, such as PVT, have also been used [see, e.g., International PCT Application No. WO 90/03844]. Numerous other formats are presently available, and any format may be modified for use herein by including one or more recording devices.

Detailed Description Text (441):
Further, as shown in the Examples, the recording device may be coated with glass, etched and the coated with a layer of scintillant. The scintillant may be formed from a polymer, such as polyacrylamide, gelatin, agarose or other suitable

material, containing fluophors, a scintillation cocktail, FlexiScint [Packard Instrument Co., Inc., Downers Grove, Ill.] NE Technology beads [see, e.g., U.S. Pat. No. 4,588,698 for a description of the preparation of such mixtures]. Alternatively, microplates that contain recording devices in one or more wells may be coated with or impregnated with a scintillant or microplates containing scintillant plastic may be manufactured with recording devices in each well. If necessary, the resulting bead, particle or continuous matrix, such as a microplate, may be coated with a thin layer polystyrene, TEFLON or other suitable material. In all embodiments it is critical that the scintillant be in sufficient proximity to the linked molecule or biological particle to detect proximate radioactivity upon interaction of labeled molecules or labeled particles with the linked molecule or biological particle.

Detailed Description Text (542):
Mixtures nucleic acid probes linked to the matrices with memories can be used for screening in assays that heretofore had to be done with one probe at a time or with mixtures of probes followed by sequencing the hybridizing probes. There are numerous examples of such assays [see, e.g., U.S. Pat. No. 5,292,874, "Nucleic acid probes to Staphylococcus aureus" to Milliman, and U.S. Pat. No. 5,232,831, "Nucleic acid probes to Streptococcus pyogenes" to Milliman, et al.; see, also, U.S. Pat. Nos. 5,216,143, 5,284,747 5,352,579 and 5,374,718]. For example, U.S. Pat. No. 5,232,831 provides probes for the detection of particular Streptococcus species from among related species and methods using the probes. These probes are based on regions of Streptococcus rRNA that are not conserved among related Streptococcus species. Particular species are identified by hybridizing with mixtures of probes and ascertaining which probe(s) hybridize. By virtue of the instant matrices with memories, following hybridization, the identity of the hybridizing probes can be determined by querying the memories, and thereby identifying the hybridizing probe.

Detailed Description Text (549):
Methods of DNA sequencing based on hybridization of DNA fragments with a complete set of fixed length oligonucleotides [usually 8-mers] that are immobilized individually as dots in a 2-dimensional matrix is sufficient for computer-assisted reconstruction of the sequences of fragments up to 200 bases long [International PCT Application WO 92/10588]. The nucleic acid probes are of a length shorter than a target, which is hybridized to the probes under conditions such that only those probes having an exact complementary sequence are hybridized maximally, but those with mismatches in specific locations hybridize with a reduced affinity, as can be determined by conditions necessary to dissociate the pairs of hybrids. Alignment of overlapping sequences from the hybridizing probes reconstructs the complement of the target [see, EP 0 535 242 A1, International PCT Application WO 95/00530, and Khrapko et al. (1989) FEBS Lttrs. 256:118-122]. The target fragment with the sequence of interest is hybridized, generally under highly stringent conditions that tolerate no mismatches or as described below a selected number of mismatches, with mixtures of oligonucleotides [typically a mixture of octomers of all possible sequences] that are each immobilized on a matrix with memory that is encoded with the sequence of the probe. Upon hybridization, hybridizing probes are identified by routine methods, such as OD or using labeled probe, and the sequences of the hybridizing probes can be determined by retrieving the sequences from the linked memories. When hybridization is carried out under conditions in which no mismatches are tolerated, the sequence of the target can then be determined by aligning overlapping sequences of the hybridizing probes.

Detailed Description Text (558):
In other embodiments, the transfer medium [i.e., the nitrocellulose or other such medium] may be part of the surface of the chip or array of chips that can bind to the separated species subsequent to separation. For example, the separation system, such as the agarose or polyacrylamide gel, can be included on the surface(s) of the matrix with memories in the array. After separation the surface will be activated

with a photoactivatable linker or suitable activating agent to thereby covalently link, such as by a photoflash, the separated molecules to the matrices in the array.

Detailed Description Text (559):
Alternatively, each matrix with memory may have one or more specific binding agents, such as an antibody or nucleic acid probe, attached (adsorbed, absorbed, or otherwise in physical contact) to matrix with memory. The matrix with memory and linked binding agent is then contacted with a medium containing the target(s). After contacting, which permits binding of any targets to which the linked binding agents specifically bind, the matrix with memory is processed to identify memories with matrices to which target has specifically bound via interaction with the binding agent. For example, the (1) the target is labeled, thereby permitted direct detection of complexes; (2) the memory with matrix is then contacted with a developing agent, such as a second antibody or detection probe, whereby binding agent-target complexes are detected; or (3) the detection agent is present during the reaction, such as non-specifically attached to the matrix with memory or by other method [thin film, coated on the matrix with memory, coated on nitrocellulose].

Detailed Description Text (890):
A variety of small molecules, such as biotin, peptides, and oligonucleotides, may be synthesized on the MICROTUBE microvessel [see, e.g., scheme 2 (biotin), below]. In order to reduce steric hindrance and improve the interaction of labeled biological target (e.g. antibody, receptor, and complementary DNA or RNA, labeled probe), and depending on the size and nature of the small molecule, different percentages of the functional groups were used for chemical synthesis while the remaining functional group(s) were blocked with Boc. Conditions in which 0.25% to 100% of the functional groups were used for chemical synthesis were evaluated. The results indicated that use of 25% of the functional groups for chemical synthesis is optimal.

Detailed Description Text (904):
A variety of the labeled probes (e.g., fluorescence and radiolabels) may be used to detect the identity of a synthesized oligonucleotide on the surface of the polymer, which has been radiation grafted [see, below] on the MICROTUBE microvessel (or on a particle in a MICROKAN microreactor]. Oligonucleotides may be also characterized using a labeled complementary DNA or RNA in a hybridization assay.

Other Reference Publication (20):
Urdea, et al., "A comparison of non-radioisotopic hybridization assay methods using fluorescent, chemiluminescent and enzyme labled synthetic oligodeoxyribonucleotide probes", Nucl. Acids. Resh., 16(11):4937-4957, 1988.

Other Reference Publication (104):
Aoki et al., Effect of quaternization on electron diffusion for redox hydrogels based on poly(4-vinylpyridine), J. Phys. Chem. 99:(14)5102-5110, (1995).

Other Reference Publication (184):
Towbin et al., Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: Procedure and some applications, Proc. Natl. Acad. Sci. USA, 76(9):4350-4354 (1979).

Other Reference Publication (375):
Padwa et al., Photocycloaddition of arylazirenes with electron-deficient olefins, J. Am. Chem. Soc. 93(2):548-550 (1971).

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L11: Entry 26 of 36 File: USPT Feb 23, 1999

DOCUMENT-IDENTIFIER: US 5874214 A
**** See image for Certificate of Correction ****
TITLE: Remotely programmable matrices with memories

Detailed Description Text (4):
As used herein, a matrix refers to any solid or semisolid or insoluble support to which the memory device and/or the molecule of interest, typically a biological molecule, organic molecule or biospecific ligand is linked or contacted. Such materials include any materials that are used as affinity matrices or supports for chemical and biological molecule syntheses and analyses, such as, but are not limited to: polystyrene, polycarbonate, polypropylene, nylon, glass, dextran, chitin, sand, pumice, teflon, agarose, polysaccharides, dendrimers, buckyballs, polyacrylamide, silicon, rubber, and other materials used as supports for solid phase syntheses, affinity separations and purifications, hybridization reactions, immunoassays and other such applications. The matrix herein may be particulate or may be in the form of a continuous surface, such as a microtiter dish or well, a glass slide, a silicon chip, a nitrocellulose sheet, nylon mesh, or other such materials. When particulate, typically the particles have at least one dimension in the 5-10 mm range or smaller. Such particles, referred collectively herein as "beads", are often, but not necessarily, spherical. Such reference, however, does not constrain the geometry of the matrix, which may be any shape, including random shapes, needles, fibers, elongated, etc. Roughly spherical "beads" are presently preferred. The "beads" may include additional components, such as magnetic or paramagnetic particles [see, e.g., Dyna beads (Dynal, Oslo, Norway)] for separation using magnets, as long as the additional components do not interfere with chemical reactions, data entry or retrieval from the memory.

Detailed Description Text (35):
As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography [TLC], mass spectrometry [MS], size exclusion chromatography, gel electrophoresis, particularly agarose and polyacrylamide gel electrophoresis [PAGE] and high performance liquid chromatography [HPLC], used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

Detailed Description Text (41):
As used herein, Southern, Northern, Western and dot blot procedures refer to those in which DNA, RNA and protein patterns, respectively, are transferred for example, from agarose gels, polyacrylamide gels or other suitable medium that constricts convective motion of molecules, to nitrocellulose membranes or other suitable medium for hybridization or antibody or antigen binding are well known to those of skill in this art [see, e.g., Southern (1975) J. Mol. Biol. 98:503-517; Ketner et al. (1976) Proc. Natl. Acad. Sci. U.S.A. 73:1102-1106; Towbin et al. (1979) Proc. Natl. Acad. Sci. U.S.A. 76:4350].